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Green and Reusable Nanocatalyst for the Synthesis of 1,5-benzodiazepines and Its Derivatives under Solvent-free Conditions

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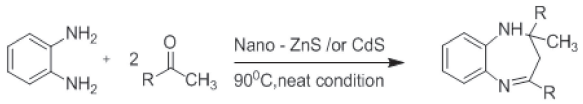
Novel, reusable, and efficient (Cd, Zn) S nanocatalysts were prepared by simple and economical chemical bath deposition using a greener approach. The as-synthesized catalysts were characterized by XRD, SEM, TEM, and FT-IR spectroscopy. The catalytic activity of as-prepared nanocatalysts were examined for the synthesis of 1,5-benzodiazepines and its derivatives under solvent-free conditions without using any toxic materials. It has been observed that CdS nanocatalyst shows superior catalytic activity and is recyclable and reusable for ten runs without any significant loss.

Benzodiazepines and their derivatives have received significant attention due to their remarkable central nervous system depressant activity and are now known to be one of the most widely prescribed classes of psychotropics.[1] They are broadly used as antibiotics, and in various diseases such as cancer, viral infection (HIV), and cardiovascular disorders and also useful in the treatment of anxiety, insomnia, agitation, seizures, muscle spasms, alcohol withdrawal and as a premedication for medical or dental procedures.[2,3] The 1,5-benzodiazepine core is found in compounds active against a variety of target types such as peptide hormones, interleukin converting enzymes, and potassium blockers. Furthermore, benzodiazepines also act as valuable intermediates in the synthesis of fused ring compounds such as triazolo-, oxadiazolo-, oxazino-, and furanobenzodiazepines.[4] 1,5-Benzodiazepines are generally synthesized by acid-catalyzed condensation of *o*-phenylenediamines with ketones. From the reported literature, the synthesis of benzodiazepines includes usage of various metal salts, CAN, heteropolyacids, ionic liquids, etc.[5–8] However, most of these processes have certain limitations, such as prolonged reaction time, use of strong acid or organic solvents, generation of by-products, anhydrous conditions, poor yields, and tedious work-up procedures. Therefore, improvements in this synthesis have been sought continuously. In recent years, there has been an upsurge of interest on the usage of heterogeneous nanocatalyst because of their quantum size effect that leads to increase in relative number of surface atoms and thus improvement in catalytic activity.[9] The usage of ZnS and CdS semiconductor nanoparticles in biomedical applications has been studied.[10] However, there are very few reports on the synthesis of 1,5-benzodiazepines and their derivatives using nanocatalyst.[11]

In this article, we report the synthesis and characterization of ZnS and CdS nanoparticles and examined the feasibility of catalytic activity in the synthesis of 1,5-benzodiazepines and their derivatives using the process of condensation of σ-phenylenediamine with various ketones under solvent-free conditions (Scheme 1).



Scheme 1.

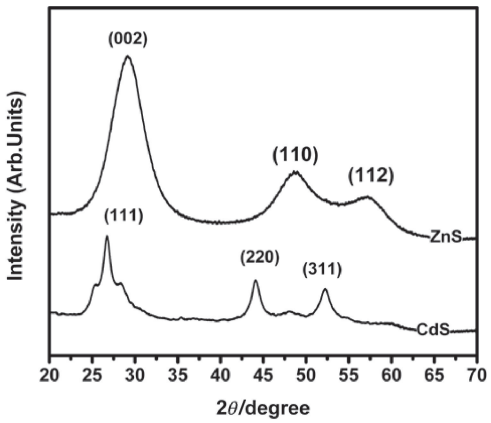


Figure 1. XRD patterns for ZnS and CdS nanoparticles.

ZnS and CdS nanoparticles were synthesized by simple chemical bath deposition of $Zn(CH_3COO)_2$ (zinc acetate)/cadmium acetate dihydrate $(Cd(OAc)_2)\cdot 2H_2O$, trisodium citrate, NaOH and thiourea solution and ethylene glycol containing PVP near room temperature (ca. 35 °C). The product was separated from the reaction mixture by centrifugation, washed several times with ethanol and finally treated with 0.1 M HNO_3. The detailed experimental method is given in Supporting Information (SI). The morphological, structural, chemical, and optical properties of ZnS and CdS nanoparticles were analyzed with SEM, XRD, EDAX, TEM, and FTIR techniques.

The XRD pattern (Figure 1) of ZnS nanoparticles exhibits diffraction peaks which are significantly broadened because of very small crystalline size. The ZnS nanoparticles exhibit hexagonal structure (JCPDS No. 80-0007) with preferred orientation (002) along with (110), and (112) directions. The crystalline size of ZnS nanoparticles and CdS nanoparticles was calculated using the Scherrer formula and was found to be about 5 and 8 nm respectively, indicating their nanocrystalline nature. On the other hand, XRD pattern of CdS nanoparticles exhibits cubic phase with preferred orientation (111) along with (220), (311) directions. No metal or other phases were detected by XRD for ZnS and CdS nanoparticles.

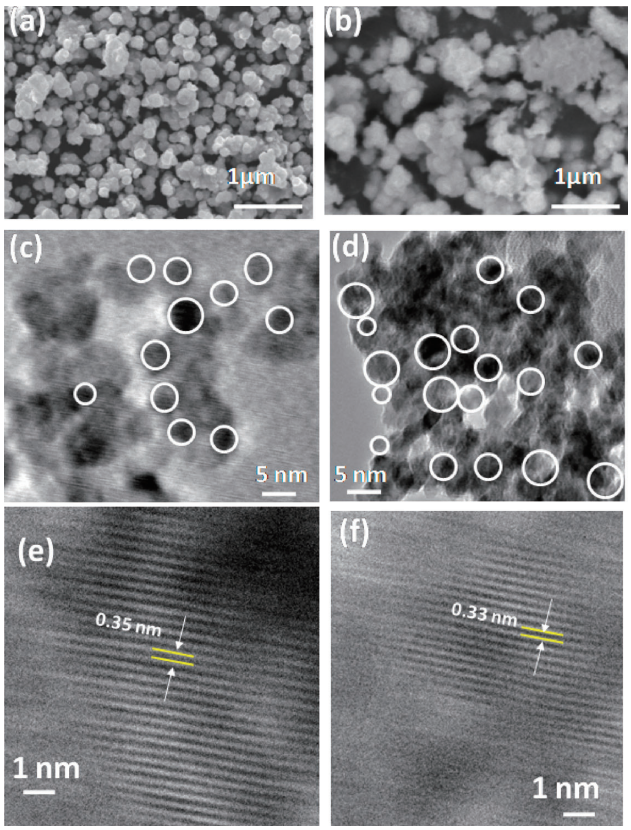


Figure 2. (a), (b) SEM, (c), (d) TEM, and (e), (f) HRTEM images of ZnS and CdS nanoparticles respectively.

The surface morphology and chemical composition of the ZnS and CdS nanoparticles (Figures 2a and 2b) were observed by scanning electron microscopy (SEM). Figure 2a shows ZnS nanospheres having rough surface composed of agglomerated nanoparticles with an average diameter of about 70 nm. The presence of some larger particles attributes to aggregation or overlapping of smaller particles. Figure 2b shows the spherical-shaped CdS nanoparticles aggregated with small particles due to growth and assembly of CdS nuclei. The chemical composition of synthesized ZnS and CdS nanoparticles were analyzed by EDS which was given in Figures 1 and 2 in SI.

On further investigation, the sizes of ZnS and CdS nanoparticles were analyzed by TEM (Figures 2c and 2e) and it reveals that the ZnS nanoparticles (Figure 2c) were 3–5 nm in diameter. From HRTEM image, the interplanar spacing was about 0.35 nm (Figure 2e) and it represents (002) lattice plane of hexagonal wurtzite structure of ZnS nanoparticles. Figure 2d indicates the TEM images of CdS nanoparticles. TEM image clearly revealed that the synthesized CdS nanoparticles (Figure 2d) have particle size of 6–8 nm. From HRTEM image, the interplanar spacing was known to be about 0.33 nm (Figure 2f) and it represents (111) lattice plane of cubic structure of CdS nanoparticles. The sizes of CdS and ZnS nanoparticles were corroborated with XRD results. The reason for the appearance of aggregates of both sulfide (CdS and ZnS) nanoparticles was possibly due to static attraction of their surface groups. Figure 3 in SI, shows the FTIR spectra of synthesized CdS nanoparticles, which were prepared by chemical bath deposition. From the FTIR data, bands around 3000–3600 cm^{-1} representing (OH) stretching vibrations and bands at 1620 cm^{-1} due to (HOH) bending vibrations seems to be in good agreement with the reported values.[12] In addition, the group of peaks around 1000 cm^{-1} was an indicative of sulfate groups, which has been previously reported for water on bulk sulphides.[13] There were medium to strong absorption bands at 613 and 723 cm^{-1} which have been assigned to Cd–S stretching.[14] However, there has been no evidence of distinct ZnO and/or CdO phase from diffraction data and the FTIR data, thereby indicating that the oxidized groups were confined to the nanoparticle surface.

Table 1. Comparison of various bulk catalysts with nanocatalyst for the condensation of *o*-phenylenediamine with acetone (ketone) under solvent-free conditions (Scheme1)[a]

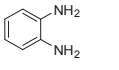
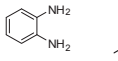
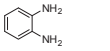
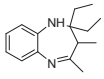
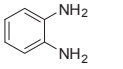
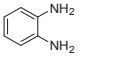
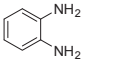
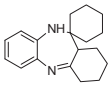
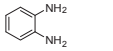
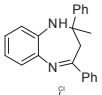
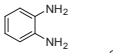
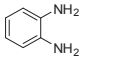
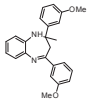
Entry	Catalyst	Time /min	Yield /%[b]
1	$ZnSO_4$	25	57
2	$CdSO_4$	25	61
3	Bulk ZnO commercial	25	67
4	Bulk ZnS commercial (100 nm)	30	69
5	Bulk CdS commercial (100 nm)	30	73
6	Nano-ZnS 5%	25	88
7	Nano-CdS 5%	20	92
8	Nano-CdS 10%	20	98
9	Nano-CdS 20%	16	98

[a]Reaction conditions: *o*-phenylenediamine (1 mmol), acetone as ketone (2 mmol), and catalyst (10 mol %), solvent free, temperature 90 °C. [b]Based on isolated yield.

This study was initiated by testing the catalytic activity of ZnS and CdS nanoparticles in comparison with commercial catalysts for the synthesis of 1,5-benzodiazepines by condensation of σ-phenylenediamine with acetone as ketone under solvent-free condition as shown in Table 1. Commercial salts i.e., $ZnSO_4 \cdot 7H_2O$ and $CdSO_4 \cdot 7H_2O$ catalysts with an amount of 5% (Table 1, Entries 1 and 2) exhibit poor yield and, bulk ZnO, ZnS, and CdS (commercial, size ca. 0.1 µm) giving (Entries 3–5) moderate yields. It has been observed that among the bulk commercial catalyst CdS shows higher yield compared to ZnO and ZnS. On the other hand, ZnS and CdS nanocatalysts (prepared in our lab, Entries 6–8) show excellent yield in short reaction time. The increased catalytic activity of nanoparticles over commercial catalyst may be attributed to higher surface area, thus resulting in higher surface concentration of the reactive sites. The theoretically calculated surface area of bulk CdS and nano CdS are 12.42 and 155.27 $m^2 g^{-1}$ respectively. However, there was no significant improvement in yield when above 10 mol % (Entry 9) amount of catalyst was used in the reaction.

To study the viability of the synthetic method for preparing benzodiapine derivatives, different ketones were readily reacted with *o*-phenylenediamine. The scope and generality of this process was illustrated with various cyclic and acyclic ketones, and the results were summarized in Table 2. Based on electrophilic nature, the alkyl, cyclic, and aromatic ketones gives higher yields (Table 2). For instance, treatment of phenylenediamine with different cyclic and alkyl-substituted ketones, acetone exhibits higher yields (Table 2, Entry 1) compared to remaining alkyl-substituted ketones because of the more electrophilic centre of acetone for the nucleophilic *o*-phenylenediamine. For the same reason, aromatic methyl-substituted ketones, phenyl acetone exhibits higher yields (Table 2, Entry 7) compared to remaining ketones.

Table 2. The condensation of *o*-phenylenediamine with ketones in the presence of nano-CdS[a]

S.No	Diamine	Ketone	Product	Reaction time/min	Yield[b] /%
1				20	98
2				25	93
3				20	95
4				20	94
5				20	95
6				25	88
7				16	96
8				20	93
9				30	88

[a]Reaction conditions: *o*-phenylenediamines (1 mmol), ketones (2 mmol), and catalyst (10 mol %), solvent free, temperature 90 °C. [b]Based on isolated yield.

The reusability of CdS nanocatalyst in the synthesis of 1,5-benzodiazepines by condensation of σ-phenylenediamine with ketone under solvent-free conditions was studied. After completion of the condensation of dimethyl ketone with *o*-phenylenediamine, the reaction mixture was diluted with ethyl acetate and the catalyst was recovered by filtration. The solid-supported catalyst was dried in an oven and reused for subsequent experiments under similar reaction conditions.

The catalyst maintained its good level of efficiency even after being reused for ten runs (Figure 3). The product was obtained in 98, 95, 93, 92, and 91% yields after successive cycles. The observed fact was that yields of the product remained comparable in these experiments and established the recyclability and reusability of the catalyst without any significant loss in activity. The slight loss of catalytic efficiency was most likely due to the loss of catalyst during the handling i.e., recovering, washing, and reusing. It was observed that there is no significant change in morphology and size of the CdS nanoparticles before reaction and after nine cycles (Figure 4, SI).

In conclusion, we have synthesized CdS nanoparticles as a new heterogeneous catalyst for the synthesis of xanthenes and their derivatives without using acidic catalyst, solvent, or toxic materials with superior catalytic activity in short reaction time. In addition, nano CdS offers the competitive advantage of easy workup and easy separation from the reaction mixture to be reused and the recyclability of the catalyst without significant degradation

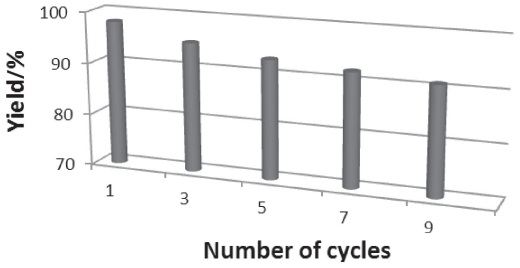


Figure 3. Reusability of CdS nanoparticles.

of catalytic activity, These results proved that CdS nanocatalyst provides the development of green synthesis of 1,5-benzodiazepines and their derivatives under solvent-free conditions, fast reaction rates, mild reaction conditions, good yields, and the reaction seems to be economically and potentially valuable for industrial applications.

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Supporting Information is available electronically on J-STAGE.

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